Gustavo Correia Ribeiro
Licenciado em Bioquímica

Multicomponent synthesis of highly functionalized pyridin-2(1*H*)-ones

Dissertação para obtenção do Grau de Mestre em
Química Bioorgânica

Orientador: Artur Manuel Soares Silva, Prof. Dr., Universidade de Aveiro
Manuela Marques Araújo Pereira, Dra., Universidade Nova de Lisboa

Presidente: Prof.Doutora Paula Cristina de Sério Branco
Arguente: Prof.Doutora Maria Manuel Martinho Sequeira Barata Marques

FACULDADE DE CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

Setembro 2015

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Agradecimentos

Primeiro quero agradecer ao meu orientador Professor Doutor Artur Silva pela disponibilidade e pela oportunidade que me disponibilizou, sem ele teria sido impossível realizar este trabalho.

Agradeço também muito aos Doutores Samuel Guieu e Raquel Seixas pela ajuda que me deram, pelo conhecimento que me transmitiram e pela imensa paciência que demonstraram para lidar comigo. Mais uma vez sem vocês esta tese seria impossível.

Agradeço também à Professora Doutora Paula Branco por me ter apoiado durante este mestrado e, entendendo a minha situação, mesmo assim acreditou que eu acabaria as cadeiras todas e terminaria este trabalho.

Aos meus amiguinhos e amiguinhas em Lisboa deixo agradecimentos e saudades estes anos foram óptimos e é difícil arranjar amigos como vocês.

Aos meus amigos do secundário agradeço pelos anos de amizade que me deram e pela preparação para o que estava por vir.

Agradeço também aos meus colegas de trabalho no pingo doce, dificilmente pagaria as propinas se não tivessem acreditado em mim e me apoiado.

Aos meus colegas de laboratório agradeço a ajuda que me deram e a disponibilidade que apresentaram.

Finalmente agradeço à Nina por me ter apoiado durante este ano mesmo nos dias piores.

Abstract

A multicomponent reaction (MCR) is a one-pot reaction of three or more starting compounds to form a single product. We used a MCR between 3-formylchromone, Meldrum's acid and a primary amine to form a pyridone ring. A pyridone is a nitrogen heterocycle containing a carbonyl group. We scanned the optimal conditions of the reaction by varying the solvent, the temperature, the concentration and the amount of reagents. The reaction achieved high yields and two pyridone final products were obtained, one with a carboxylic acid using methanol as solvent at room temperature, and the other, without the carboxylic acid, when the reaction was carried out in refluxing water with tetrabutylammonium bromide. Using the optimal conditions for the purpose of study the reaction mechanism and more importantly the reaction range of possible products, we scoped the reaction by varying the amine and the diketone-like reagent. The results show that Meldrum's acid is important for the reaction, but the amine can add variability to the reaction.

Keywords

Multicomponent reaction
3-Formylchromone
Pyridin-2(1*H*)-one

Resumo

Uma reacção multicomponente (RMC) é uma reacção entre três ou mais compostos iniciais para formar um produto. Usámos uma RMC entre 3-formilcromona, ácido de Meldrum e uma amina primária para formar um anel de piridin-2(1*H*)-ona. Uma piridin-2(1*H*)-ona é um heterociclo de azoto contendo um grupo carbonilo na posição 2. Testámos as condições óptimas para a reacção variando o solvente, a temperatura, a concentração e a quantidade de reagentes. A reação originou com bom rendimento duas piridin-2(1*H*)-onas, uma com um ácido carboxílico usando metanol como solvente à temperatura ambiente, e outra sem o ácido carboxílico, quando a reação foi realizada numa solução aquosa de brometo de tetrabutilamónio a refluxo. Usando as condições óptimas para o estudo do mecanismo da reacção e, mais importante, da variabilidade de novos produtos, testou-se a reacção com diferentes aminas e dicetonas. Os resultados mostram que o ácido de Meldrum é importante para a reacção, mas a amina pode adicionar variabilidade a esta reacção.

Palavras-chave

Reação multicomponente
3-Formilcromona
Piridin-2(1*H*)-ona

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Abbreviations and Symbols

Ar – Aromatic

Ac – Acetyl

br – Broad

Bu – Butyl

COSY – Correlation Spectroscopy

^{13}C NMR – Carbon-13 nuclear magnetic resonance

d – Doublet

dd – Doublet of doublets

ddd – Double doublet of doublets

DMAD – Dimethyl acetylenedicarboxylate

DMF - *N*,*N*-Dimethylformamide

ESI^{+}-MS – Positive-ion electrospray ionisation mass spectra

ESI^{+}-HRMS – Positive-ion electrospray ionisation high resolution mass spectra

HMQC – Heteronuclear Multiple-Quantum Correlation

^{1}H-NMR – Proton nuclear magnetic resonance

J – Coupling constant

MCR – Multicomponent reaction

Me – methyl

m – Multiplet

Ph – Phenyl

rt – Room temperature

s – Singlet

TBAB – Tetrabutylammonium bromide

TLC – Thin-layer chromatography

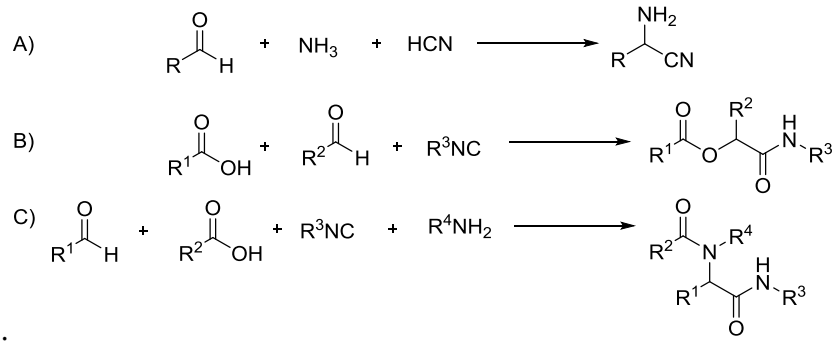
t – Triplet

δ – Chemical shift

1 Introduction

1.1 Multicomponent Reactions

A multicomponent reaction (MCR) is a one-pot reaction of three or more starting compounds to form a single product with the majority of the atoms of the starting material. It is (in a way) the opposite of a multistep sequential synthesis of a molecule. The starting compounds react in a sequence of elementary steps, instead of reacting simultaneously in one step. The multicomponent reaction are especially variable, with many different reactions possible, they are also easier to carry out than multistep synthesis.[1] Some examples of multicomponent reactions are the synthesis of aminonitriles in the Strecker synthesis (scheme 1.1 A),[2] the formation of a peptide bond in the Passerini reaction (scheme 1.1 B)[3] and the heavily used and studied Ugi reaction by an isocyanide, a carboxylic acid, a primary amine and an aldehyde (scheme 1.1 C)[1].



Scheme 1.1. Examples of multicomponent reactions

Multicomponent reactions can also be combined, resulting in more complex and specialized reactions, and allowing for a larger array of drug synthesis. Multicomponent reactions can also be very dependent of metallic catalysts like palladium, copper or nickel,[4] raising their rate and viability.

1.2 Chromones and pyridones

Pyridones

Pyridones are six-membered nitrogen heterocycles, bearing a carbonyl group and two double bonds. They can have substituents in any of the ring carbons and in the nitrogen atom. The pyridone ring also tends to be associated to other aromatic rings in natural and synthetic compounds.

Examples of the occurrence of pyridin-2(1*H*)-one rings in natural compounds are the anti-tumor antibiotic diazaquinomycin A found in a *Streptomyces sp.* isolated from riverbank soil in Manitoba, Canada (figure 1.1, a)[5] and the alkaloid pyridin-2(1*H*)-one named Ricinine present in a plant (*Ricinus communis*, picture 1.1*)* that works as an insecticidal and hepatotoxic compound (figure 1.1, b).[6] Pyridin-2(1*H*)-one rings can also be found in many synthetic drugs, like pyridone L-697.661 (figure 1.1, c) that can act as a specific non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus-1 (HIV-1), or Milrinone and Amrinome that work as cardiotonic agents for the treatment of heart failure (figure 1.1, d,e).[7]

Picture 1.1 *Ricinus communis*

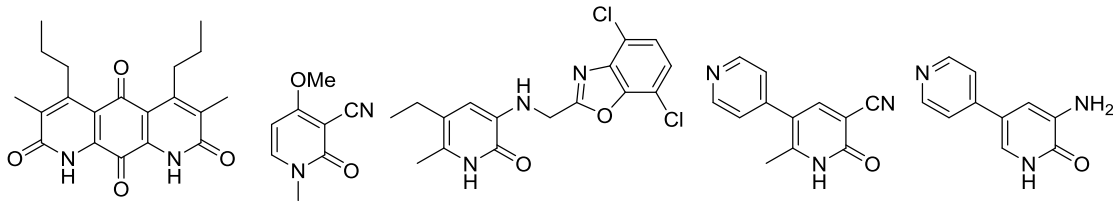


Fig 1.1 Natural and synthetic pyridin-2(1*H*)-ones

Pyridones can have many uses due to their vast list of chemical properties and a range of possible reactions. Normally they are either pyridin-4(1*H*)-ones or pyridin-2(1*H*)-ones depending where the amine is positioned in the semi-aromatic ring (figure 1.2). Pyridin-4(1*H*)-ones can be used, for example, as ligands in europium nitrate complexes.[8] Pyridin-2(1*H*)-ones have many properties like their ambident nucleophilic nature that will control the alkylation of the molecule. This ambident nature can depend on many factors like the structure of the alkyl halides, the substituents on the ring, the solvent or the temperature of the reaction.[9]

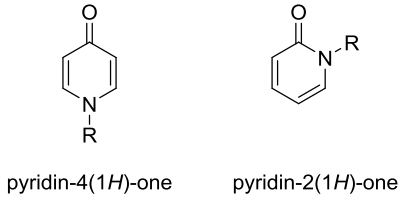
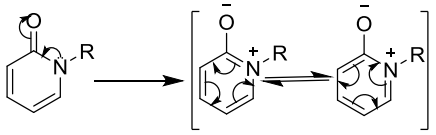


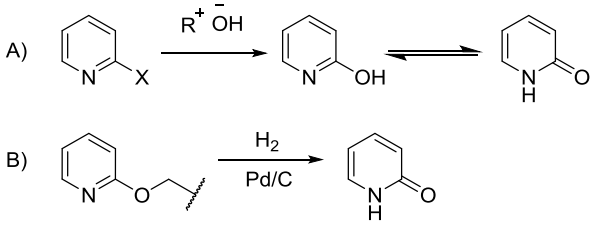
Fig 1.2 Structure of the pyridone isomers

Another relevant property of pyridones is the semi-aromatic ring, like showed in scheme 1.2.



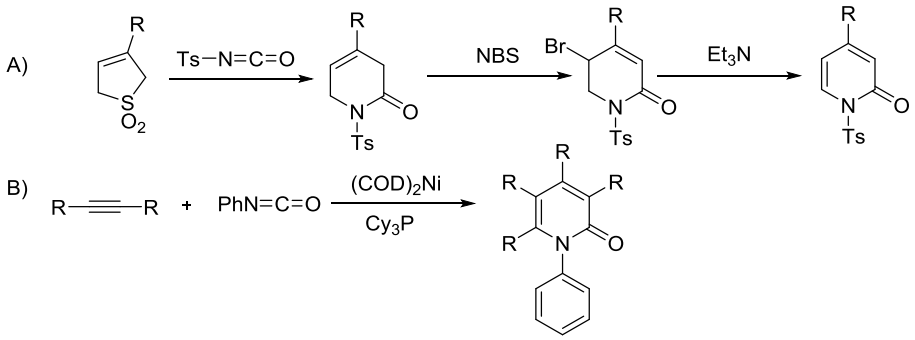
Scheme 1.2 Semi-aromatic character of the pyridin-2(1*H*)-one ring

The synthesis of pyridin-2(1*H*)-ones can occur by three methods: using a pyridine ring, cycloaddition and cyclization reactions.[10] The first method focus on the similarities between the pyridine ring and pyridone compounds. An addition of a carbonyl group to the ring can be achieved in numerous reactions, normally, either by nucleophilic substitution of a halogenated pyridine (with the help or not of a catalyst) (scheme 1.3 A)[11] or by reduction of an alkoxy pyridine (scheme 1.3 B).[12]



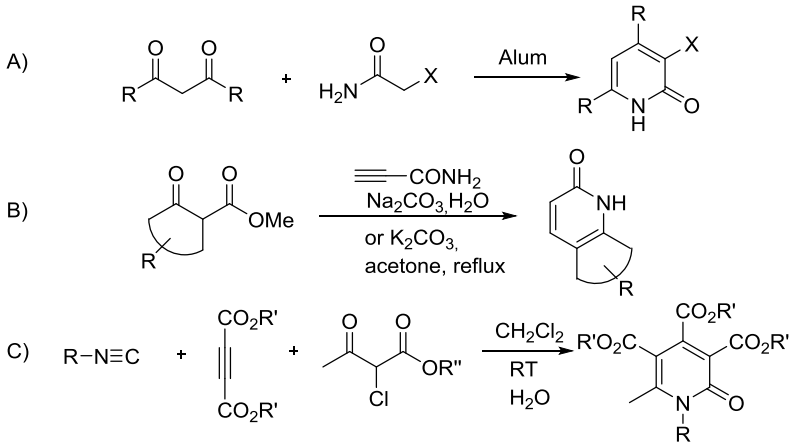
Scheme 1.3 Synthesis of pyridin-2(1*H*)-ones using pyridines as starting materials

Cycloaddition reactions in the synthesis of pyridones are normally Diels-Alder reactions (scheme 1.4 A),[13] but they can be other more uncommon reactions, for example the Nickel-catalyzed addition of alkynes to an amide to form a pyridone cycle (scheme 1.4 B).[14]



Scheme 1.4 Synthesis of pyridin-2(1*H*)-ones by cycloaddition reactions

The third method for synthesis of pyridin-2(1*H*)-ones involves the cyclization of acyclic compounds. The array of cyclization reactions is large, which can be a simple addition of alkyl groups to diketones (scheme 1.5 A)[15] or total synthesis of a polyene chain with a pyridin-2(1*H*)-one ring (figure 1.3).[16] These reactions can also give products with specific characteristics, like pyridin-2(1*H*)-one fused rings (scheme 1.5 B),[17] or be based on very common reactions like multicomponent reactions (scheme 1.5 C).[18]



Scheme 1.5 Synthesis of pyridin-2(1*H*)-ones by cyclization of acyclic compounds

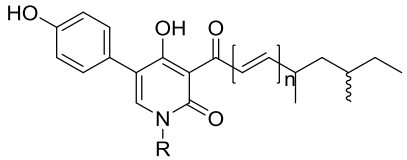
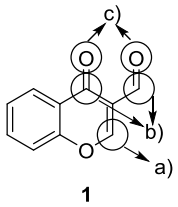


Fig 1.3 Polyene chain with a pyridin-2(1*H*)-one ring

Chromones

Chromones are polycyclic organic compounds with a benzene ring and a six-membered oxygen heterocycle bearing a carbonyl group. Due to its chemical properties and easy access, 3-formylchromone **1** was chosen as the precursor for our multicomponent reaction (figure 1.4).[19]

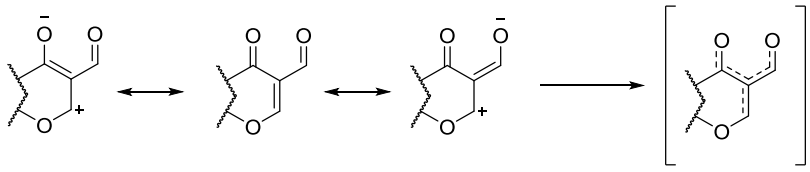


1

Fig 1.4 Reactive centers in 3-formylchromone 1

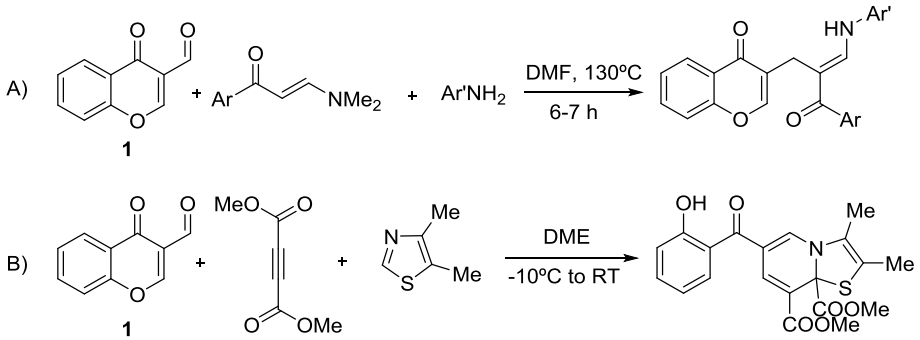
The 3-formylchromone **1** has three main reactive sites:

a) The β-carbon from the ketone, which lacks electron density due to the ketone and aldehyde carbonyl groups and the oxygen from the ether group. This, coupled with the effect of delocalized electrons, that I will be explaining more in detail later, creates a very reactive electrophilic carbon.
b) The two electrophilic ketone and aldehyde carbonyl groups, these carbonyl groups together with the carbon-2 form a delocalization of electrons, which allows the formation of more stable transition states and a faster intermolecular charge transfer, this is illustrated in Scheme 1.6.
c) The oxygen atoms of the ketone and aldehyde groups are nucleophilic and therefore are another reactive part of the molecule.



Scheme 1.6 Delocalization of charge in the 3-formylchromone 1 ring

As examples of multicomponent reactions using 3-formylchromone **1** as starting material, one can referred to that presented by Prasanna et al., giving a carbonyl arylamino chromone by a Michael addition, a nucleophilic attack and a deoxygenation (scheme 1.7 A),[20] or a one-pot reaction forming a heterocyclic compound with 4,5-dimethylthiazole and DMAD as shown by Terzidis et al. (scheme 1.7 B).[21]



Scheme 1.7 Multicomponent reactions using 3-formylchromone 1

Our purpose is to create and study a successful multicomponent reaction using 3-formylchromone **1** as its main reagent, an amine (*p*-anisidine **2**) and Meldrum's acid **3**. This diester (Meldrum's acid **3**) has an unusually high acidity, thermal instability and a tendency to dissociate, forming carbon dioxide and/or an acetone molecule depending of the reaction.[22]

We choose to study a multicomponent reaction of 3-formylchromone due to the double electrophilic centers and general reactivity of this compound. Diketones are good nucleophiles with electrophilic centers being bifunctional molecules. Since the final product was meant to be a nitrogen compound, we used primary amines as nucleophiles (Figure 1.5).

To start our multicomponent reaction study we choose Meldrum's acid and *p*-anisidine because they are strong nucleophiles.

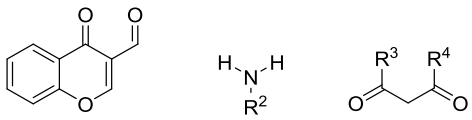
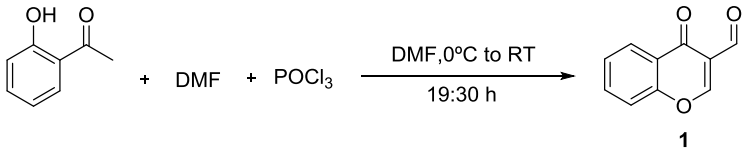


Fig 1.5 General scheme of the proposed reaction

2. Results and discussions

2.1 Synthesis of 3-formylchromone

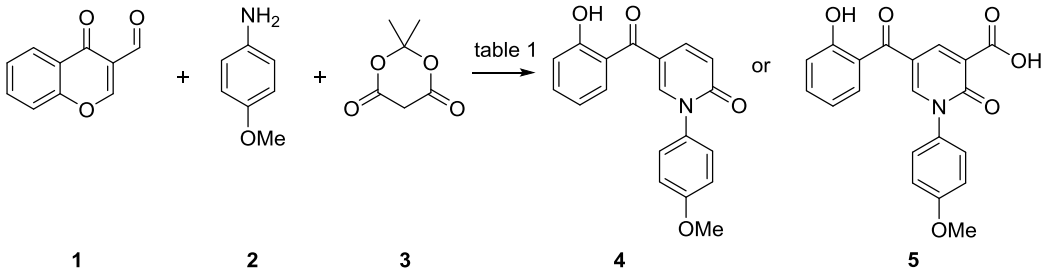
The starting material, 3-formylchromone **1**, was synthetized by the Vilsmeier-Haack formylation reaction described in the literature,[24] of the 2'-hydroxyacetophenone with *N*,*N*-dimethylformamide (DMF) and phosphoryl oxychloride ($POCl_3$), at 0ºC and for 19:30 h (scheme 2.1). This reaction gave a good yield (80%), and the obtained solid was used for all further reactions.



Scheme 2.1 Synthesis of 3-formylchromone 1

2.2 Optimization of the reaction conditions

The study of this reaction started with the optimization of the experimental conditions for 3-formylchromone **1**, Meldrum's acid **3** and *p*-anisidine **2** (Scheme 2.2).



Scheme 2.2 Synthesis of pyridin-2(1*H*)-ones 4 and 5

To achieve the perfect conditions for the synthesis of pyridin-2(1*H*)-one **4** we started our study screening the reaction solvents. Solvents with different polarity and proticity characteristics were chosen. Acetonitrile was used as polar aprotic solvent, toluene as a non-polar solvent, 1,2,4-trichlorobenzene as a non-polar solvent with a high boiling point and methanol and water as polar protic solvents. All the reactions were performed with one molar equivalent of each reagent and heated at a temperature close to the boiling point of each solvent (table 1, entries 3, 4, 5, 6, 7, 8). Another two reactions were made in the absence of solvent (neat), only mixing the reagents or grinding them (table 1, entries 1, 2).

Table 2.1 Optimization of the reaction conditions.

Entry	Equivalents 1/2/3	Solvent	[1] (M)	Temp.(ºC)	Time	Product (Yield)
1	1/1/1	Neat	0.2	130ºC	0.5 h	**4** (30%)
2	1/1/1	Neat (grind)	0.2	130ºC	0.5 h	**4** (27%)
3	1/1/1	CH_3CN	0.2	reflux	24 h	**4** (26%)
4	1/1/1	Toluene	0.2	reflux	24 h	**4** (51%)
5	1/1/1	1,2,4-Trichlorobenzene	0.2	reflux	3 h	**4** (29%)
6	1/1/1	H_2O	0.2	reflux	24 h	**4** (45%)
7	1/1/1	H_2O + TBAB (0.2 M)	0.2	reflux	24 h	**4** (66%)
8	1/1/1	MeOH	0.2	reflux	1.33 h	**5** (44%)
9	1/1.2/1.2	MeOH	0.2	reflux	2 h	**5** (53%)
10	1/1.2/1.2	MeOH	0.2	RT	2 h	**5** (53%)
11	1/1.5/1.5	MeOH	0.2	RT	2 h	**5** (64%)
12	1/1.2/1.2	H_2O + TBAB (0.2 M)	0.2	reflux	24 h	**4** (83%)
13	1/1.2/1.2	H_2O + TBAB (0.2 M)	0.2	RT	24 h	**5** (-)[a]
14	1/1.2/1.2	H_2O + TBAB (0.2 M)	0.2	60ºC	24 h	**5** (-)[a]
15	1/1.2/1.2	H_2O + TBAB (0.2 M)	0.1	reflux	24 h	**4** (76%)
16	1/1.2/1.2	H_2O + TBAB (0.1 M)	0.2	reflux	24 h	**4** (52%)
17	1/1.2/1.2	H_2O + TBAB (0.3 M)	0.2	reflux	24 h	**4** (82%)

[a] The compound was identified by ^{1}H NMR of the crude reaction.

All the solvents tested, with exception of methanol, lead to the same product, pyridin-2(1*H*)-one **4**. Better yields were obtained in water and toluene (45% and 51%, respectively) than in acetonitrile and 1,2,4-trichlorobenzene (26% and 29%, respectively). When water was used as solvent, the reagents and the product of the reaction were unable to dissolve, so in order to overcome this problem, TBAB was added to improve their solubility (table 1, entries 7, 12).

Better yield was obtained when using a 0.2 M solution of TBAB in water (66% instead of 45%). Performing the reaction in the absence of solvent did not give better results and, in an attempt to improve the yield, we grind the compounds to raise the contact between them and aid the melting process, however the yield of both reactions was similar, probably due to difficulty in grinding the reagents (30% and 27%, respectively). The obtained results in the study of the solvent suggest that the reaction is more effective in protic polar solvents, with exception of methanol.

In methanol, using an excess of *p*-anisidine **2** and Meldrum's acid **3** (1.2 equiv.) we slightly increased the yield of pyridin-2(1*H*)-one **5** from 44% to 53% (table 1, entries 8, 9). When 1.5 equiv. of *p*-anisidine **2** and Meldrum's acid **3** were used a better yield of product **5** was obtained (64%). Optimization of the reaction conditions was also achieved by lowering the temperature to room temperature, giving us the best conditions for this reaction (table 1, entries 9, 10, 11).

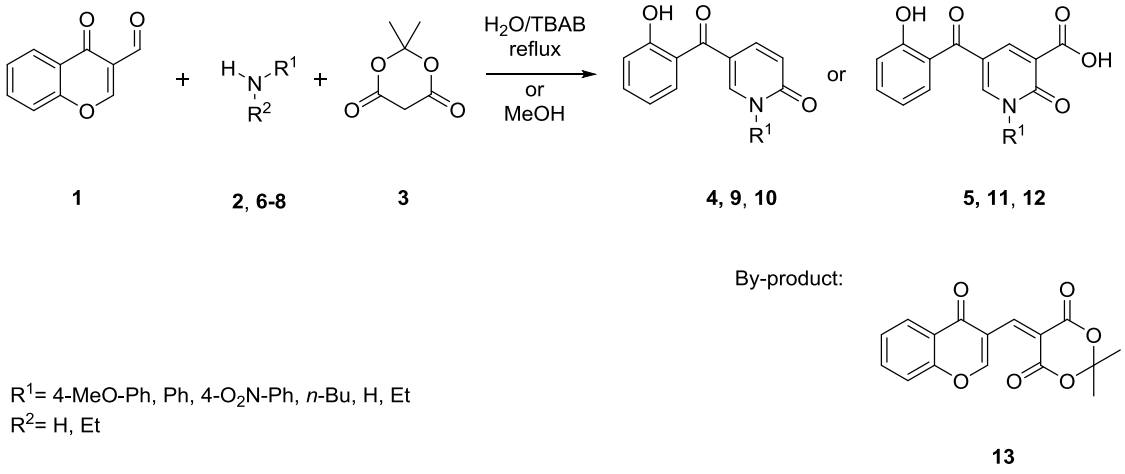
Similar to the reaction in methanol, when the solvent used was water in the presence of TBAB (0.2 M) the excess of *p*-anisidine **2** and Meldrum's acid **3** (1.2 equiv.) improved the yield of pyridin-2(1*H*)-one **4** to 83% (table 1, entries 7, 12). When this reaction was performed at room temperature or 60ºC, decarboxylation did not occur and pyridin-2(1*H*)-one **5** was formed instead of **4**. This compound was identified by ^{1}H NMR of the crude reaction and the yield was not calculated because the amount of product synthetized was not enough to purify and separate it from TBAB (table 1, entries 13, 14).

To optimize the concentration of TBAB in water, we performed the reaction with two different concentrations of TBAB (0.1 M and 0.3 M). As expected the decrease of the concentration of TBAB decreased the solubility of the reagents and therefore the yield of the reaction (from 83 to 52%, table 1, entries 12, 16). The increase of TBAB to 0.3 M did not improved the yield (83% to 82%, table 1, entries 12, 17), being the ideal concentration of TBAB for the synthesis of pyridin-2(1*H*)-one **4** 0.2 M.

We also lowered the concentration of 3-formylchromone **1** from 0.2 to 0.1 to test the dilution effect in the reaction yield. The yield decreased from 83% to 76% (table 1, entries 12, 15) probably due to the smaller probability of 3-formylchromone **1** molecules that collide with the other reagents. This implies that the ideal concentration is 0.2 M.

2.3 Scope of the multicomponent reaction of 3-formylchromone: changing the amine

With the best conditions in hand for the multicomponent reaction, the scope of the reaction was investigated, first by varying the amine. We tested various amines to study the extension of the reaction of synthesis of pyridin-2(1*H*)-one **4** and **5** (Scheme 2.3).



1 **2, 6-8** **3** **4, 9, 10** **5, 11, 12** **13**

Scheme 2.3 Synthesis of pyridin-2(1*H*)-ones and by-product by varying the amine

First we tested two other aromatic amines instead of the electron donor aromatic amine already used (*p*-anisidine **2**). Aniline **6** was used as an example of an aromatic amine without any substituent and 4-nitroaniline **7** was used as an aromatic amine with an electron withdrawing group in the *para* position. The butylamine **8** was used as an aliphatic non-polar amine, ammonia as an amine with no substituents and diethylamine as a secondary amine.

In both conditions, aromatic amines with electron donating substituents gave better yields (table 2, entries 1-4). Higher yields were obtained in H_2O/TBAB [pyridin-2(1*H*)-one **4**, **9**, **10**] than in methanol [pyridin-2(1*H*)-one **5**, **11**, **12**]. 4-Nitroaniline **7** was unreactive, due to its strong electron withdrawing group, the only product obtained was **13** (table 2, entries 5, 6). Chromone **13** is the result of a Knoevenagel condensation of 3-formylchromone **1** with the Meldrum's acid **3**.

The studied reaction is also suitable for alkylamines and as an example we used *n*-butylamine **8**. Indeed, the expected butylpyridin-2(1*H*)-one **10** and **12** were obtained in good yields in both reaction conditions (table 2, entries 7, 8).

Table 1.2 Scope of the reaction with different amines

Entry	Amine	R^1	R^2	Conditions	Product (Yield)
1	**2**	4-MeO-Ph-	H	H_2O/TBAB, reflux	**4** (83%)
2	**2**	4-MeO-Ph-	H	MeOH, RT	**5** (64%)
3	**6**	Ph	H	H_2O/TBAB, reflux	**9** (50%)
4	**6**	Ph	H	MeOH, RT	**11** (40%)
5	**7**	4-O_2N-Ph-	H	H_2O/TBAB, reflux	Mixture of compounds
6	**7**	4-O_2N-Ph-	H	MeOH, RT	**13** (64%)
7	**8**	*n*-Bu	H	H_2O/TBAB, reflux	**10** (74%)
8	**8**	*n*-Bu	H	MeOH, RT	**12** (62%)

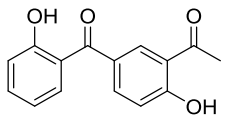
In order to prepare unsubstituted pyridin-2(1*H*)-ones we attempt the reaction with ammonia (ammonium hydroxide 25% was used), although no pyridin-2(1*H*)-one was observed.

In an attempt to formulate a reaction mechanism and to identify which carbon (C-2' or C-4/C-6) of chromone **13** is attacked by the amine, we did a reaction with diethylamine, but no intermediary compound was observed. However, from this reaction we only obtained mixtures of inseparable compounds that we were not able to identify.

2.4 Scope of the multicomponent reaction of 3-formylchromone: changing the diketone

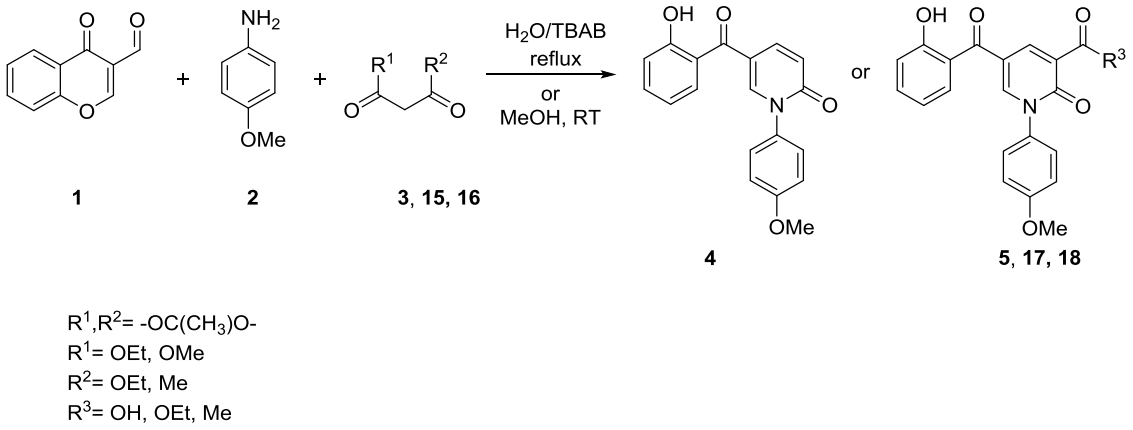
We tested various diketones to study the extension of the reaction of synthesis of compound **4** and **5** (Scheme 2.4).

First we tested a reaction of 3-formylchromone **1**, *p*-anisidine **2** and acetylacetone as its diketone, in neat, for 30 minutes and at 130ºC. This reaction gave the compound **14** (figure 2.1) already described in the literature[23] in 5% yield.



14

Fig 2.1 Structure of 1-[2-hydroxy-5-(2-hydroxybenzoyl)phenyl]ethan-1-one 14



Scheme 2.4 Synthesis of pyridin-2(1*H*)-ones by varying the diketone starting material

First we tested two compounds, **15** and **16**, with ester groups that are similar to the Meldrum's acid **3** used in the first reaction. Using these starting materials we obtained low yields (29% and 32%, table 3, entries 3, 5), proving that the cyclic structure of Meldrum's acid **3** improves significantly the reaction. It is worth to notice that the yields obtained using these diketones are almost the same meaning both have similar reactivity.

Table 2.2 Scope of the reaction with different diketones

Entry	Diketonate	R^1	R^2	Conditions	Product (Yield)
1	**3**	Meldrum's acid		H_2O/TBAB, reflux	**5** (83%)
2	**3**	Meldrum's acid		MeOH, RT	**6** (64%)
3	**15**	OEt	OEt	H_2O/TBAB, reflux	**17** (29%)
4	**15**	OEt	OEt	MeOH, RT	Mixture of compounds
5	**16**	OMe	Me	H_2O/TBAB, reflux	**18** (32%)
6	**16**	OMe	Me	MeOH, RT	Mixture of compounds

The third diketone tested had two aromatic groups (1,3-di-*p*-tolylpropane-1,3-dione), allowing us to test the lack of reactive ester groups in the reaction. 4-Hydroxycoumarin has a structure similar to Medrum's acid but also an aromatic ring, while malononitrile instead of ester groups has two nitrile groups. However the reactions with these diketones lacking the ester reactive groups (tolylpropan-1,3-dione, 4-hydroxycoumarin and malononitrile) originate a mixture of compounds, giving no pure product.

Finally only the reactions in water with TBAB gave products, possibly because some of the reaction conditions may not be ideal for less reactive diketones.

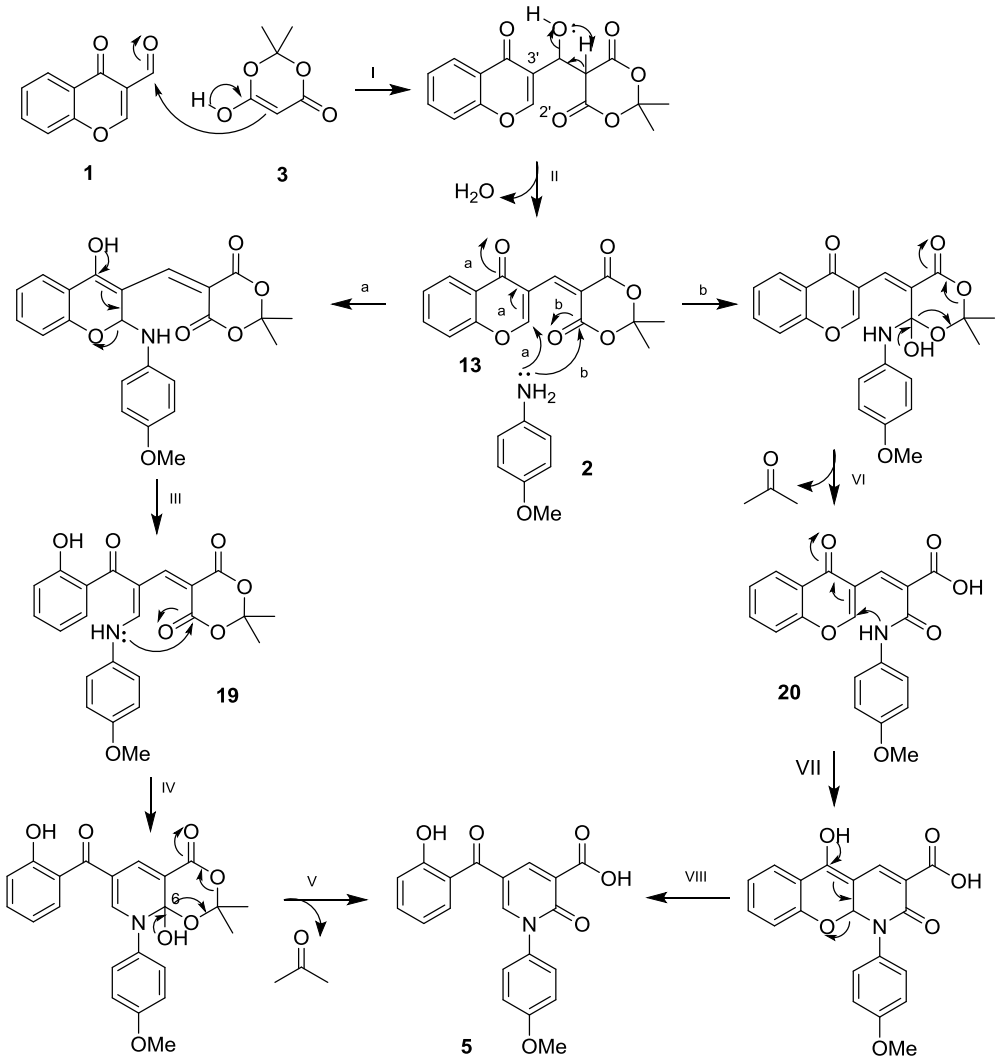
2.5 Reaction mechanism

Taking into account the results from the screening of conditions and from the different amines and diketones used, the proposed mechanism for the main synthesis of pyridin-2(1*H*)-one **4** is depicted in Scheme 2.5.

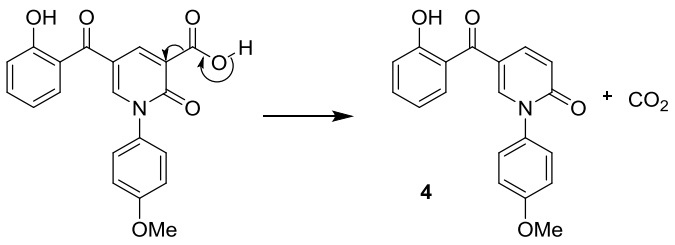
The first step of this reaction is the formation of chromone **13**, by 1,2-addition of Meldrum's acid **3** to 3-formylchromone **1**, followed by elimination of water, because this compound was formed using different amines, even with a non-reactive amine, while with a non-reactive diketone, no main product was synthetized. We can assume that Meldrum's acid **3** is the preferred nucleophile and even if the imine compound is formed (with 3-formylchromone **1** and *p*-anisidine **2**) it is attacked by the Meldrum's acid **3** and compound **13** is formed. The formation of product **13** also clearly shows that between all the reactive points of the 3-formylchromone **1**, the aldehyde group is the most reactive and the one attacked by the enolic form of Meldrum's acid **3**, as showed in scheme 2.5.

Product **13** is then the basis for the second stage of the main reaction. This stage has four parts, addition of the amine (where the reactivity of the amine is more relevant), opening of the chromone ring, formation of the pyridone ring and dissociation of the Meldrum's acid ring. The addition of the amine to chromone **13** is started by the attack of the non-ligand electron pair of the nitrogen to the C2'' of the chromone, that results in the opening of the chromone ring leading to the alcohol group in the aromatic ring of the molecule (scheme 2.5, a). The next step is the formation of the pyridone ring by a nucleophilic attack of the amine to the carboxyl group of the Meldrum's acid moiety. Finally the reaction ends with opening of the Meldrum's acid ring, with loss of acetone and formation of pyridin-2(1*H*)-one **5**. This chain reaction is the result of an unstable quaternary carbon (carbon C6) formed in the cyclization step.

An alternative proposal to this mechanism considers the nucleophilic attack of the amine to the carboxyl group of the Meldrum's acid followed by ring opening and loss of an acetone leading to the intermediate **20**. Formation of the pyridone ring by nucleophilic attack of amine to C6 with opening of the chromone ring gives pyridin-2(1*H*)-one **5**.



Scheme 2.5 Proposed mechanism for the synthesis of pyridin-2(1*H*)-one 5.



Scheme 2.6 Proposed mechanism for decarboxylation.

In order to prepare the intermediary **19** or **20** we attempt the reaction with diethylamine, but only inseparable compounds that we were not able to identify were obtained. With the results from the reactions it is not possible to choose one of the pathways because neither the intermediate **19** nor the intermediate **20** was observed.

Refluxing pyridin-2(1*H*)-one **5** in water/TBAB (0.2 M), was performed to prove that the decarboxylation occurred in the last step of the reaction, since gave pyridin-2(1*H*)-one **4** in high yield (89%).

2.6 Example of NMR analysis

To illustrate an analysis of the nuclear magnetic resonance (NMR) spectra peaks, and assign the protons and carbons of the molecule, we are going to use the ^{1}H NMR and ^{13}C NMR of 5-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one **4**.

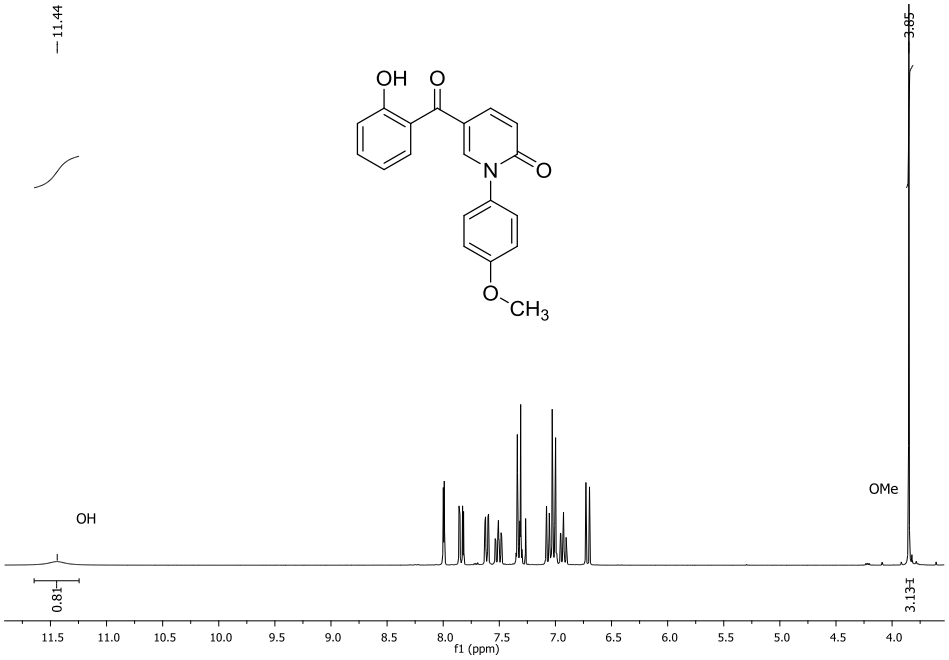


Fig 2.2 ^{1}H NMR spectrum of 5-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one 4.

The first easily recognizable signals are the broad singlet at 11.44 ppm that is very deshielded due to being a OH proton with a hydrogen-bond, and the singlet at 3.85 ppm, that corresponds to the OMe protons, because it appears in the aliphatic zone and integrate to three protons (Figure 2.2). The remaining signals (between 8.5 ppm and 7.5 ppm) correspond to the aromatic protons of the compound.

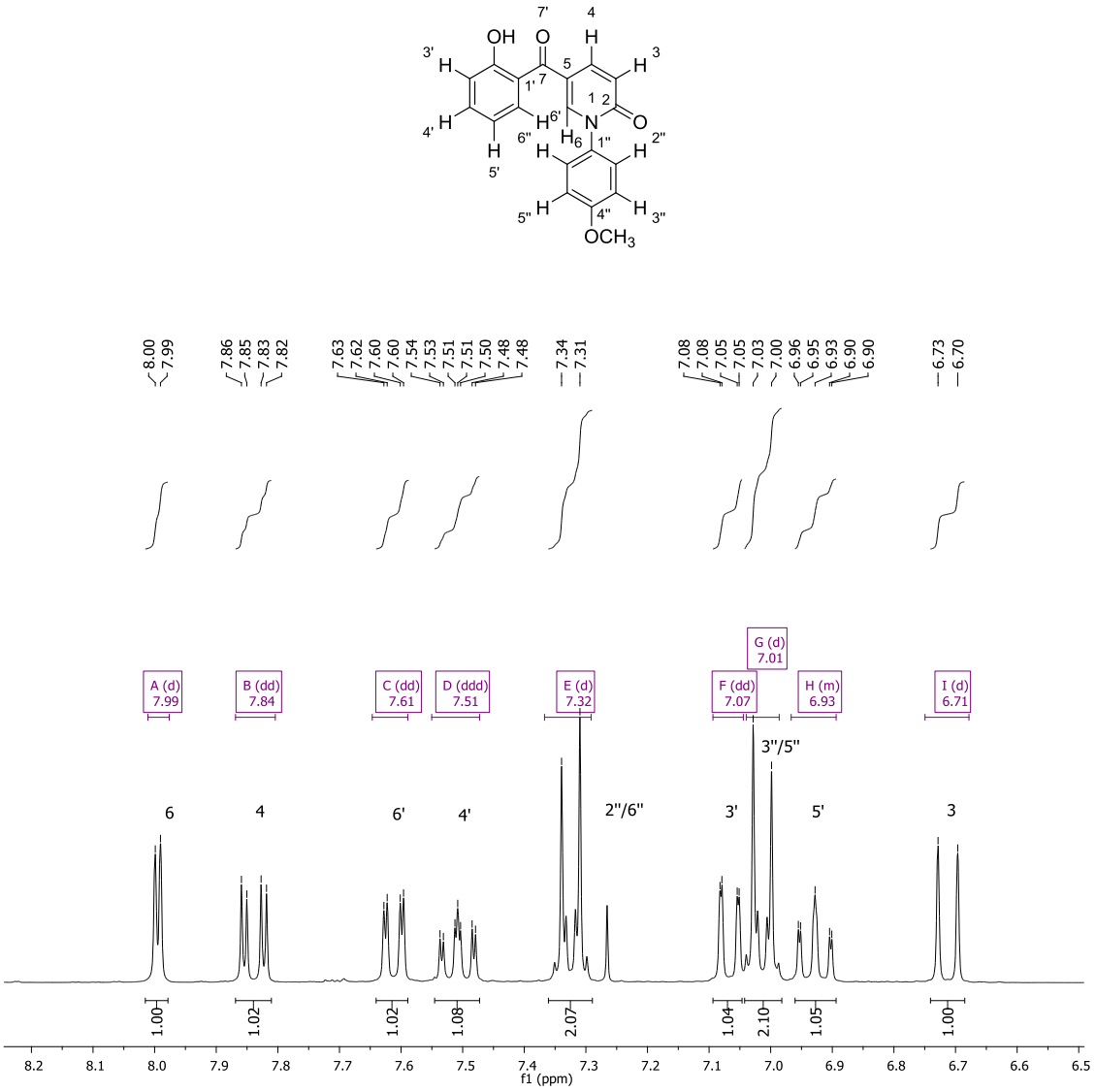


Fig 2.3 ^{1}H NMR spectrum of 5-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one 4, aromatic signals.

Of the aromatic protons, the first to be identified are the aromatic protons from the 4-methoxyphenyl ring, due to their integration to 2 and coupling constant (8.7 Hz) typical of *orto* coupling. These doublets have a chemical shift of 7.32 and 7.01 ppm, being the last one correspondent to H-3''/5'' due to the resonance shielding effect of methoxyl group. The next proton is a doublet at 7.99 ppm with a coupling constant of 2.5 Hz typical with *meta* coupling. This leads to the conclusion that the proton is the one isolated in the pyridone ring (H-6, fig 2.3). This coupling constant is shared by a double doublet at 7.94 ppm meaning this value refers to proton H-4 (fig 2.3). The higher coupling constant from this double doublet helps identify the proton H-3 that is a doublet at 6.71 ppm.

The final four protons from the pyridone have a peculiar multiplicity, two are double doublets at 7.61 and 7.07 ppm, and the other two are double doublet of doublets at 7.51 and 6.93

ppm. This relates to the aromatic ring structure, with the more centered protons (H-4' and H-5') having higher multiplicity and the other two protons (H-3' and H-6') with lower multiplicity.

In the carbon attribution the first carbon (at 195.2 ppm), being so much deshielded can only be the C=O carbon between the rings (C-7). The next three signals are the other carbons that have a bound with an oxygen atom and no hydrogen (Figure 2.4). In the next five carbons only the signal at 132.8 ppm can be assigned to carbon C-1'' due to the lower intensity and chemical shift, the other can only be assigned by 2D analysis.

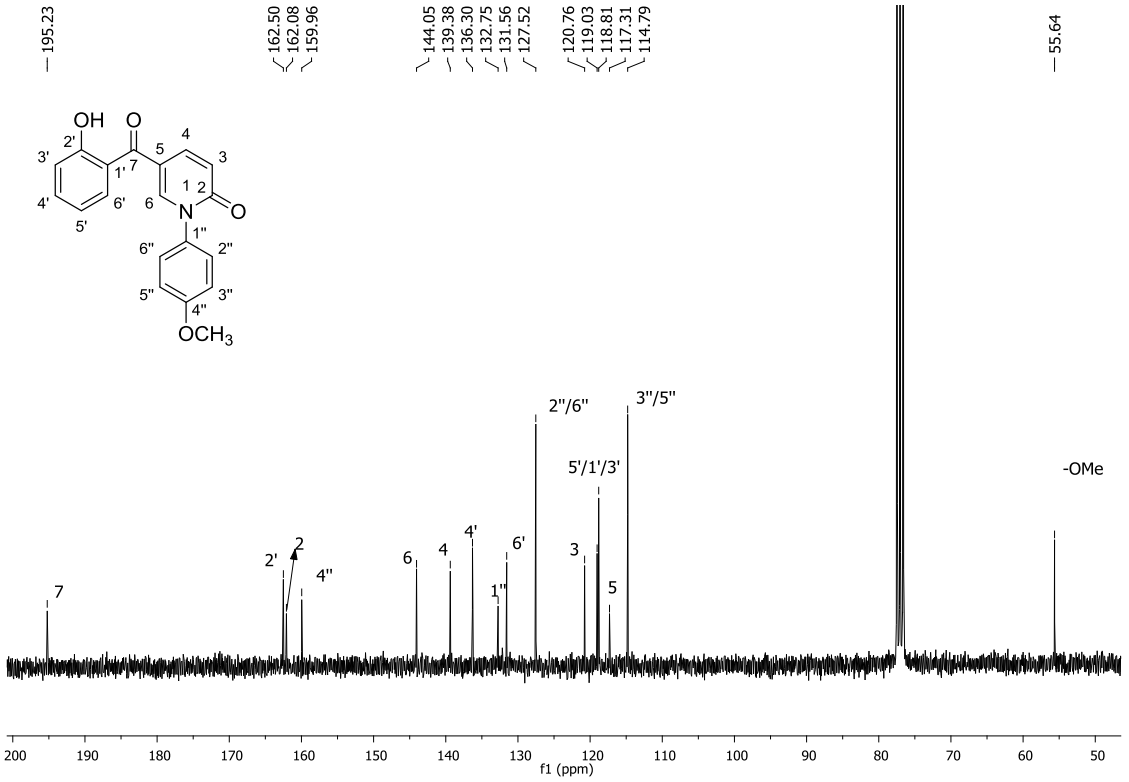


Fig 2.4 ^{13}C NMR spectrum of 5-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one 4.

At 127.5 ppm and 114.8 ppm we find two signals with high intensity (double the intensity of other signals), leading to the conclusion that they each refer to two carbons instead of one, each signal corresponding to two carbons with equal chemical surroundings. These four carbons are those that have a proton in the aromatic ring of the amine. The other signal that is easily identifiable is at 55.6 ppm, because with such a low chemical shift this carbon can only be from the –OMe group in the 4-methoxyphenyl ring. The other carbons cannot be assigned by simple ^{13}C NMR analysis. Further specification of the protons and carbons of the pyridone was done by 2D *g*HSQC and *g*HMBC.

When the ^{1}H and ^{13}C spectra from pyridin-2(1*H*)-one **4** are compared with those from pyridin-2(1*H*)-one **5** we observe that the proton from the carboxylic acid can be seen and the previous doublet signal at 6.71 ppm that corresponds to proton H-3 disappears. Also the signal

at 7.94 ppm that was a double doublet became a doublet due to losing the coupling with proton H-3.

In the carbon spectra, there is one more carbon signal from the carboxylic acid group, at 164.5 ppm.

3. Conclusion

A multicomponent reaction of 3-formylcromone **1**, a primary amine and Meldrum's acid **3** was successful to prepare pyridones in high yields. The reaction conditions were studied and the optimal reaction conditions were obtained, involving refluxing water with TBAB (0.2 M) for 24h to give pyridin-2(1*H*)-one **4**. By varying these conditions a different compound was obtained, pyridin-2(1*H*)-one **5** with a carboxylic acid group in the pyridone ring.

After this, different amines were tested to verify the effect of the amine in the reaction. The conclusion we can take is that the amine is able to induce variability in the reaction, it is only necessary to be a primary amine and is more reactive when have electron donating groups.

From the scope of the diketone we conclude that the reaction is dependent on the cyclic effect of Meldrum's acid **3** to obtain pyridones in high yield and the existence of an ester group is essential for the reaction to occur.

This work creates an alternative way for the synthesis of pyridones in relatively high yield, from commercial available or easily prepared starting materials, when compared to other pyridones synthesis, and with a large array of possible pyridone products. In the studied reaction a heterocycle ring (pyridin-2(1*H*)-one) was successfully formed from easily available primary amines by double nucleophilic attack. The decarboxylation is the last step of the reaction and is promoted by the temperature.

For the future a proposal continuation of this study is the experimentation by changing the substituents from the aromatic ring of 3-formylchromone **1** or by testing the reaction with more different amines.

Pyridones are interesting and relevant compounds, many new studies are done on pyridones nowadays and more and more chemical properties and uses are discovered. The use of a multicomponent reaction in the synthesis of pyridones makes this a fast, efficient and easy strategy, giving an economic access to new derivatives of pyridones.

4. Experimental Section

4.1 General

The commercial reagents were used without previous purification. 3-Formylchromone (**1**)[24] and 1,3-di-*p*-tolylpropane-1,3-dione[25] were prepared according to the procedures described in the literature. Solvents used in reactions and purifications were analytically pure. The evolution of the reactions was controlled by thin-layer chromatography (TLC), in plastic sheets coated in silica gel 60G F_{254}. Preparative thin-layer chromatography was carried out in silica plates (20 x 20 cm) and previously coated with a thin-layer of silica gel 60G F_{254} from Merck, with 0.5 mm of thickness and activated in a oven at 100 ºC for 12 hours. After elution the plates were observed in UV light at λ = 254 and/or 366 nm.

Melting points were determined on a Büchi Melting Point B-540 apparatus and are uncorrected. NMR spectra were recorded on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) spectrometer, using $CDCl_3$ or Acetone-d_6 as solvent. Chemical shifts (δ) are reported in ppm values and coupling constants (*J*) in Hz. The internal standard was TMS. ^{1}H assignments were made using 2D NOESY (800 ms mixing time) experiments, while ^{13}C assignments were made using 2D *g*HSQC and *g*HMBC (long-range C/H coupling constants were optimized to 7 Hz) experiments. Positive-ion ESI mass spectra (HRMS and MS) were acquired using a LTQ Orbitrap XL mass spectrometer (Thermo Fischer Scientific, Bremen, Germany) controlled by *LTQ Tune Plus 2.5.5* and *Xcalibur 2.1.0*. The capillary voltage of the electrospray ionization was set to 3100 V. The capillary temperature was 275ºC. The sheath gas flow rate (nitrogen) was set to 5 (arbitrary unit as provided by the software seetings). The capillary voltage was 36 V and the tube lens voltage 110 V.

4.2 General experimental procedures

Procedure 1: Multicomponent reaction using water/TBAB as solvent

In a sealed tube, 3-formylchromone **1** (1 equiv., 0.2 mmol, 34.8 mg) was suspended in an aqueous solution of tetrabutylammonium bromide (TBAB) (2.0 $mmol.L^{-1}$, 1 mL). The appropriated amine (1.2 equiv., 0.48 mmol) was added followed by Meldrum's acid **3** (1.2 equiv., 0.48 mmol, 34.6 mg) and the reaction mixture was refluxed for 24 h. The reaction was cool down to room temperature and the product was extracted with CH_2Cl_2 (3 x 2 mL). The

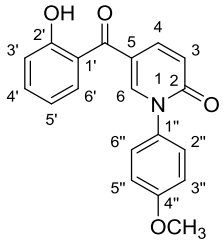
organic phases were combined, washed with water (3 x 2 mL) to remove the TBAB, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (eluent: CH_2Cl_2/EtOAc, 90/10).

Procedure 2: Multicomponent reaction using methanol as solvent

In a sealed tube, 3-formylchromone **1** (1 equiv., 0.2 mmol, 34.8 mg) was dissolved in methanol (1 mL). The appropriate amine (1.5 equiv., 0.3 mmol) was added to the solution followed by Meldrum's Acid **3** (1.5 equiv., 0.3 mmol, 43.2 mg). The solution was stirred at room temperature for 2 hours. The obtained solid was filtered and washed with methanol (3 x 1 mL). The pure pyridin-2(1*H*)-ones **5, 11-13** were obtained in good yields (40-64%) without need of purification or crystallization.

4.3 Compound list

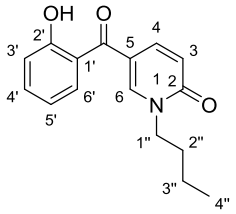
5-(2-Hydroxybenzoyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one (**4**)



Following procedure 1, using *p*-anisidine **2** compound **4** was obtained as a brown oil (53.3 mg, 83%).

^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 11.45 (br-s, 1H, 2'-O*H*), 7.99 (d, $^4J_{H\text{-}H}$ 2.5 Hz, 1H, H-6), 7.84 (dd, $^3J_{H\text{-}H}$ 9.6 Hz, $^4J_{H\text{-}H}$ 2.5 Hz, 1H, H-4), 7.61 (dd, $^3J_{H\text{-}H}$ 8.1 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-6'), 7.51 (ddd, $^3J_{H\text{-}H}$ 8.6 Hz, $^3J_{H\text{-}H}$ 7.3 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-4'), 7.33 (d, $^3J_{H\text{-}H}$ 8.7 Hz, 2H, H-2'',6''), 7.07 (dd, $^3J_{H\text{-}H}$ 8.6 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H, H-3'), 7.02 (d, $^3J_{H\text{-}H}$ 8.7 Hz, 2H, H-3'',5''), 6.93 (ddd, $^3J_{H\text{-}H}$ 8.1 Hz, $^3J_{H\text{-}H}$ 7.3 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H, H-5'), 6.72 (d, $^3J_{H\text{-}H}$ 9.6 Hz, 1H, H-3), 3.85 (s, 3H, 4''-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ =: 195.4 (*C*=O), 162.6 (C-2'), 162.2 (C-2), 160.1 (C-4''), 144.2 (C-6), 139.5 (C-4), 136.4 (C-4'), 132.9 (C-1''), 131.7 (C-6'), 127.6 (C-2'',6''), 120.9 (C-3), 119.2 (C-5'), 118.9 (2C, C-1',3'), 117.4 (C-5), 114.9 (C-3'',5''), 55.8 (4''-O*C*H_3) ppm; ESI$^+$-MS *m/z* (%) = 322 (100) $[M + H]^+$, 344 (15) $[M + Na]^+$,360 (8) $[M + K]^+$, 665 (15) $[2M + Na]^+$; ESI$^+$-HRMS *m/z* for $[C_{19}H_{15}NO_4 + H]^+$ calcd 322.1079, found 322.1067.

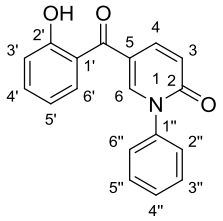
1-Butyl-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-one (**10**)



Following procedure 1, using *n*-butylamine compound **10** was obtained as a brown oil (40.2 mg, 74%);

^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 11.33 (br-s, 1H, 2'-O*H*), 7.93 (d, $^{4}J_{H\text{-}H}$ 2.6 Hz, 1H, H-6), 7.75 (dd, $^{3}J_{H\text{-}H}$ 9.5 Hz, $^{4}J_{H\text{-}H}$ 2.6 Hz, 1H, H-4), 7.54 (dd, $^{3}J_{H\text{-}H}$ 8.0 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, 1H, H-6'), 7.50 (ddd, $^{3}J_{H\text{-}H}$ 8.6 Hz, $^{3}J_{H\text{-}H}$ 7.3, $^{4}J_{H\text{-}H}$ 1.6 Hz, Hz, 1H, H-4'), 7.05 (d, $^{3}J_{H\text{-}H}$ 8.6 Hz, 1H, H-3'), 6.92 (ddd, $^{3}J_{H\text{-}H}$ 8.0 Hz, $^{3}J_{H\text{-}H}$ 7.3, $^{4}J_{H\text{-}H}$ 1.0 Hz, Hz, 1H, H-5'), 6.62 (d, $^{3}J_{H\text{-}H}$ 9.5 Hz, 1H, H-3), 3.99 (t, $^{3}J_{H\text{-}H}$ 7.4 Hz, 2H, H-1''), 1.82-1.70 (m, 2H, H-2''), 1.39 (sext, $^{3}J_{H\text{-}H}$ 7.4 Hz, 2H, H-3''), 0.96 (t, $^{3}J_{H\text{-}H}$ 7.4, 3H, H-4'') ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ = 195.3 (*C*=O), 162.5 (C-2'), 162.1 (C-2), 143.5 (C-6), 139.2 (C-4), 136.3 (C-4'), 131.7 (C-6'), 119.9 (C-3), 119.03 (C-5'), 118.96 (C-1'), 118.8 (C-3'), 117.5 (C-5), 50.7 (C-1''), 31.4 (C-2''), 19.9 (C-3''), 13.7 (C-4'') ppm; ESI^{+}-MS *m/z* (%) = 272 (100) $[M + H]^{+}$, 543 (10) $[2M + H]^{+}$; ESI^{+}-HRMS *m/z* for $[C_{16}H_{17}NO_3 + H]^{+}$ calcd 272.1287, found 272.1274.

5-(2-Hydroxybenzoyl)-1-phenylpyridin-2(1*H*)-one (**9**)

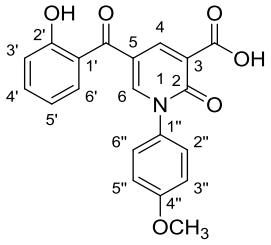


Following procedure 1, using aniline compound **9** was obtained as a brown solid (29.4 mg, 50%)

M.p.: 130-132 ºC; ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 11.37 (br-s, 1H, 2'-O*H*), 8.00 (d, $^{4}J_{H\text{-}H}$ 2.4 Hz, 1H, H-6), 7.86 (dd, $^{3}J_{H\text{-}H}$ 9.6 Hz, $^{4}J_{H\text{-}H}$ 2.4 Hz, 1H, H-4), 7.61 (dd, $^{3}J_{H\text{-}H}$ 8.1 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, 1H, H-6'), 7.63-7.47 (m, 4H, H-4',3'',4'',5''), 7.41 (dd, $^{3}J_{H\text{-}H}$ 8.1 Hz, $^{4}J_{H\text{-}H}$ 1.5 Hz, 2H, H-2'',6''), 7.07 (dd, $^{3}J_{H\text{-}H}$ 8.4 Hz, $^{4}J_{H\text{-}H}$ 1.1 Hz, 1H, H-3'), 6.93 (ddd, $^{3}J_{H\text{-}H}$ 8.1 Hz, $^{3}J_{H\text{-}H}$ 7.1 Hz, $^{4}J_{H\text{-}H}$ 1.1 Hz, 1H, H-5'), 6.75 (d, $^{3}J_{H\text{-}H}$ 9.6 Hz, 1H, H-3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ =195.3 (*C*=O), 162.6 (C-2'), 161.9 (C-2), 143.8 (C-6), 140.1 (C-1''), 139.6 (C-4), 136.4 (C-4'), 131.6 (C-6'), 129.8 (C-3'',5''), 129.4 (C-4''), 126.5 (C-2'',6''), 121.0 (C-3), 119.2 (C-

5'), 118.91 (C-3'), 118.90 (C-1'), 117.6 (C-5) ppm; ESI^+-MS *m/z* (%) = 292 (100) $[M + H]^+$, 314 (9) $[M + Na]^+$, 605 (11) $[2M + Na]^+$; ESI^+-HRMS *m/z* for $[C_{18}H_{13}NO_3 + H]^+$ calcd 292.0974, found 292.0960.

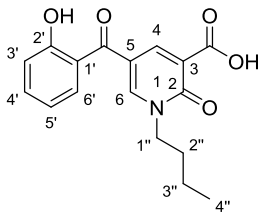
5-(2-Hydroxybenzoyl)-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**5**)



Following procedure 2, compound **5** was obtained as pale yellow crystals (38.2 mg, 53%)

M.p.: 214-216 ºC; ^{1}H NMR (300.13 MHz, Acetone-d_6, 25ºC): δ = 13.70 (br-s, 1H, 3-COO*H*), 10.95 (br-s, 1H, 2'-O*H*), 8.83 (d, $^4J_{H\text{-}H}$ 2.6 Hz, 1H, H-4), 8.56 (d, $^4J_{H\text{-}H}$ 2.6 Hz, 1H, H-6), 7.77 (dd, $^3J_{H\text{-}H}$ 7.9 Hz, $^4J_{H\text{-}H}$ 1.7 Hz, 1H, H-6'), 7.59 (d, $^3J_{H\text{-}H}$ 9.1 Hz, 2H, H-2'', 6''), 7.57 (ddd, $^3J_{H\text{-}H}$ 8.6 Hz, $^3J_{H\text{-}H}$ 7.3 Hz, $^4J_{H\text{-}H}$ 1.7 Hz, 1H, H-4'), 7.12 (d, $^3J_{H\text{-}H}$ 9.1, 2H, H-3'', 5''), 7.05 (dd, $^3J_{H\text{-}H}$ 8.6 Hz,$^4J_{H\text{-}H}$ 0.9 Hz, 1H, H-3'), 7.00 (ddd, $^3J_{H\text{-}H}$ 7.9 Hz, $^3J_{H\text{-}H}$ 7.3 Hz, $^4J_{H\text{-}H}$ 0.9 Hz, 1H, H-5'), 3.89 (s, 3H, 4''-OC*H*$_3$) ppm; ^{13}C NMR (75.47 MHz, Acetone-d_6, 25ºC): δ = 194.8 (*C*=O), 165.7 (C-2), 164.6 (3-*C*OOH), 161.6 (C-2'), 161.4 (C-4''), 149.1 (C-6), 146.0 (C-4), 136.8 (C-4'), 132.9 (2C, C-6', 1''), 128.8 (C-2'', 6''), 121.3 (C-3), 120.4 (C-5'), 119.7 (C-1'), 118.7 (C-3'), 118.4 (C-5), 115.3 (C-3'', 5''), 56.0 (-O*C*H$_3$) ppm; ESI^+-MS *m/z* (%) = 366 (38) $[M + H]^+$, 388 (100) $[M + Na]^+$, 753 (25) $[2M + Na]^+$; ESI^+-HRMS *m/z* for $[C_{20}H_{15}NO_6 + H]^+$ calcd 366.0978, found 366.0966.

1-Butyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**12**)

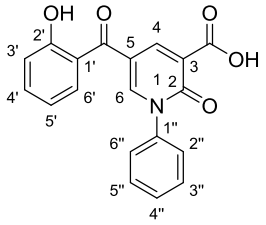


Following procedure 2, using *n*-butylamine compound **12** was obtained as pale yellow solid (39.1 mg, 62%)

M.p.: 103-105 ºC; ^{1}H NMR (300.13 MHz, $CDCl_3$, 25ºC): δ = 13.73 (br-s, 1H, 3-COO*H*), 11.30 (br-s, 1H, 2'-O*H*), 8.80 (d, $^4J_{H\text{-}H}$ 2.6 Hz, 1H, H-6), 8.25 (d, $^4J_{H\text{-}H}$ 2.6 Hz, 1H, H-4), 7.54 (ddd, $^3J_{H\text{-}H}$ 8.6 Hz, $^3J_{H\text{-}H}$ 7.2 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-4'), 7.50 (dd, $^3J_{H\text{-}H}$ 8.1 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-6'), 7.07 (dd, $^3J_{H\text{-}H}$ 8.6, $^4J_{H\text{-}H}$ 1.0, 1H, H-3'), 6.95 (ddd, $^3J_{H\text{-}H}$ 8.1 Hz, $^3J_{H\text{-}H}$ 7.2 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H,

H-5'), 4.18 (t, $^{3}J_{H\text{-}H}$ 7.4 Hz, 2H, H-1''), 1.89-1.79 (m, 2H, H-2''), 1.43 (sext, $^{3}J_{H\text{-}H}$ 7.4, 2H, H-3''), 1.00 (t, $^{3}J_{H\text{-}H}$ 7.4, 3H, H-4'') ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25ºC): δ = 194.2 (*C*=O), 164.4 (3-*C*OOH), 164.0 (C-2), 162.9 (C-2'), 146.3 (C-4), 145.1 (C-6), 137.2 (C-4'), 131.7 (C-6'), 119.6 (C-5'), 119.2 (C-3), 119.1 (C-3'), 118.3 (C-1'), 117.0 (C-5), 51.8 (C-1''), 31.2 (C-2''), 19.9 (C-3''), 13.7 (C-4'') ppm; ESI$^+$-MS *m/z* (%) = 316 (97) $[M + H]^+$, 389 (100) $[M + NH_3C_4H_9]^+$; ESI$^+$-HRMS *m/z* for $[C_{17}H_{17}NO_5 + H]^+$ calcd 316.1185, found 316.1174.

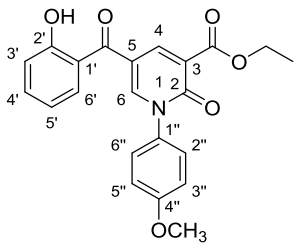
5-(2-Hydroxybenzoyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (**11**)



Following procedure 2, using aniline compound **11** was obtained as a beige solid (26.3 mg, 40%).

M.p.: 84-86 ºC; ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 13.49 (br-s, 1H, 3-COO*H*), 11.35 (br-s, 1H, 2'-O*H*), 8.97 (d, $^{4}J_{H\text{-}H}$ 2.6 Hz, 1H, H-4), 8.31 (d, $^{4}J_{H\text{-}H}$ 2.6 Hz, 1H, H-6), 7.66-7.55 (m, 5H, H-4',6',3'',4'',5''), 7.46 (dd, $^{3}J_{H\text{-}H}$ 7.5 Hz, $^{4}J_{H\text{-}H}$ 2.1 Hz, 2H, H-2'',6''), 7.11 (dd, $^{3}J_{H\text{-}H}$ 8.9 Hz, $^{4}J_{H\text{-}H}$ 1.1 Hz, 1H, H-3'), 6.98 (ddd, $^{3}J_{H\text{-}H}$ 8.5 Hz, $^{3}J_{H\text{-}H}$ 7.3 Hz, $^{4}J_{H\text{-}H}$ 1.1 Hz, 1H, H-5') ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ = 194.1 (*C*=O), 164.1 (C-2), 164.0 (3-*C*OOH), 163.1 (C-2'), 146.5 (C-6), 146.1 (C-4), 138.5 (C-1''), 137.5 (C-4'), 131.7 (C-6'), 130.6 (C-4''), 130.2 (C-3'',5''), 126.2 (C-2'',6''), 119.8 (C-5'), 119.5 (C-3), 119.3 (C-3'), 118.3 (C-1'), 117.9 (C-5) ppm; ESI$^+$-MS *m/z* (%) = 290 (100) $[M - CO_2H]^+$, 336 (29) $[M + H]^+$, 693 (12) $[2M + Na]^+$; ESI$^+$-HRMS *m/z* for $[C_{19}H_{13}NO_5 + H]^+$ calcd 336.0872, found 336.0858.

Ethyl 5-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**17**)

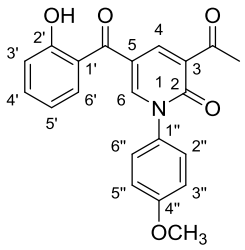


Following procedure 1, using diethyl malonate instead of Meldrum's acid compound **17** was obtained as a brown oil (23 mg, 29%).

In this case, the purification was performed using CH_2Cl_2 as eluent.

^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 11.39 (br-s, 1H, 2'-O*H*), 8.59 (d, $^4J_{H\text{-}H}$ 2.8 Hz, 1H, H-4), 8.19 (d, $^4J_{H\text{-}H}$ 2.8 Hz, 1H, H-6), 7.58 (dd, $^3J_{H\text{-}H}$ 7.5 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-6'), 7.53 (ddd, $^3J_{H\text{-}H}$ 8.5 Hz, $^3J_{H\text{-}H}$ 7.2 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-4'), 7.32 (d, $^3J_{H\text{-}H}$ 9.0 Hz, 2H, H-2'',6''), 7.08 (dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H, H-3'), 7.00 (d, $^3J_{H\text{-}H}$ 9.0 Hz, 2H, H-3'',5''), 6.95 (ddd, $^3J_{H\text{-}H}$ 7.5 Hz, $^3J_{H\text{-}H}$ 7.2 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H, H-5'), 4.38 (q, $^3J_{H\text{-}H}$ 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.85 (s, 3H, 4''-OC*H*$_3$), 1.37 (t, $^3J_{H\text{-}H}$ 7.1 Hz, 3H, OCH$_2$C*H*$_3$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ = 194.6 (*C*=O), 164.4 (3-*C*OO), 162.7 (C-2'), 160.3 (C-4''), 158.9 (C-2), 147.2 (C-6), 144.2 (C-4), 136.7 (C-4'), 132.5 (C-1''), 131.6 (C-6'), 127.7 (C-2'',6''), 121.1 (C-3), 119.4 (C-5'), 119.0 (C-3'), 118.7 (C-1'), 116.0 (C-5), 114.8 (C-3'',5''), 61.9 (O*C*H$_2$CH$_3$), 55.8 (4''-O*C*H$_3$), 14.4 (OCH$_2$*C*H$_3$) ppm; ESI$^+$-MS *m/z* (%) = 242 (98) [M – C$_6$H$_4$OCH$_3$ – OC$_2$H$_5$ + H]$^+$, 394 (100) [M + H]$^+$, 809 (11) [2M + Na]$^+$; ESI$^+$-HRMS *m/z* for [C$_{22}$H$_{19}$NO$_6$ + H]$^+$ calcd 394.1291, found 394.1278.

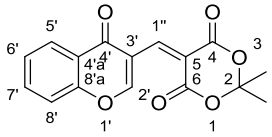
3-Acetyl-5-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one (**18**)



Following procedure 1, using methyl acetoacetate compound **18** was obtained as a black solid (23 mg, 32%).

M.p.: 84-86 Cº; ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 11.43 (br-s, 1H, 2'-O*H*), 8.58 (d, $^4J_{H\text{-}H}$ 2.8 Hz, 1H, H-4), 8.25 (d, $^4J_{H\text{-}H}$ 2.8 Hz, 1H, H-6), 7.57 (dd, $^3J_{H\text{-}H}$ 8.1 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-6'), 7.53 (ddd, $^3J_{H\text{-}H}$ 8.6 Hz, $^3J_{H\text{-}H}$ 7.6 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, 1H, H-4'), 7.33 (d, $^3J_{H\text{-}H}$ 9.0 Hz, 2H, H-2'',6''), 7.08 (dd, $^3J_{H\text{-}H}$ 8.6 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H, H-3'), 7.04 (d, $^3J_{H\text{-}H}$ 9.0 Hz, 2H, H-3'',5''), 6.95 (ddd, $^3J_{H\text{-}H}$ 8.1 Hz, $^3J_{H\text{-}H}$ 7.6 Hz, $^4J_{H\text{-}H}$ 1.0 Hz, 1H, H-5'), 3.86 (s, 3H, 4''-OC*H*$_3$), 2.71 (s, 3H, 3-COC*H*$_3$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ = 196.8 (3-*C*OCH$_3$), 194.9 (*C*=O), 162.8 (C-2'), 160.9 (C-2), 160.4 (C-4''), 147.5 (C-6), 143.3 (C-4), 136.8 (C-4'), 132.4 (C-1''), 131.7 (C-6'), 127.6 (C-2'',6''), 127.0 (C-3), 119.4 (C-5'), 119.0 (C-3'), 118.6 (C-1'), 116.9 (C-5), 115.0 (C-3'',5''), 55.8 (4''-O*C*H$_3$), 31.1 (3-CO*C*H$_3$) ppm; ESI$^+$-MS *m/z* (%) = 364 (15) [M + H]$^+$, 386 (100) [M + Na]$^+$, 749 (59) [2M + Na]$^+$; ESI$^+$-HRMS *m/z* for [C$_{21}$H$_{17}$NO$_5$ + H]$^+$ calcd 364.1185, found 364.1172.

2,2-Dimethyl-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-1,3-dioxane-4,6-dione (**13**)



Following procedure 2, using diethylamine compound **13** was obtained as a yellow solid.

M.p.: 210-212 ºC; ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 ºC): δ = 9.59 (d, $^{4}J_{H\text{-}H}$ 0.7 Hz, 1H, H-2'), 8.68 (d, $^{4}J_{H\text{-}H}$ 0.7 Hz, 1H, H-1''), 8.27 (dd, $^{3}J_{H\text{-}H}$ 8.0 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, 1H, H-5'), 7.75 (ddd, $^{3}J_{H\text{-}H}$ 8.7 Hz, $^{3}J_{H\text{-}H}$ 7.4 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, 1H, H-7'), 7.53 (d, $^{3}J_{H\text{-}H}$ 8.7 Hz, 1H, H-8'), 7.49 (ddd, $^{3}J_{H\text{-}H}$ 8.0 Hz, $^{3}J_{H\text{-}H}$ 7.4 Hz, $^{4}J_{H\text{-}H}$ 1.0 Hz, 1H, H-6'), 1.80 (s, 6H, 2-(CH_3)$_2$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 ºC): δ = 174.9 (C-4'), 163.1 (C-2'), 162.5 (COO), 160.8 (COO), 155.8 (C-8a'), 147.7 (C-1''), 134. 9 (C-7'), 126.8 (C-5'), 126.7 (C-6'), 123.8 (C-4a'), 118.6 (C-8'), 118.1 (C-3'), 116.7 (C-5), 105.2 (C-2), 27.6 (2-C(*C*H$_3$)$_2$) ppm; ESI$^+$-MS *m/z* (%) = 323 (99) [M + Na]$^+$, 623 (100) [2M + Na]$^+$; ESI$^+$-HRMS *m/z* for [$C_{16}H_{12}O_6$ + H] calcd 301.0712, found 301.0701.

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